REMARKS

Reconsideration is requested.

Claims 1-10 are pending. Claim 10 has been withdrawn from consideration. Claims 11-51 have been canceled, without prejudice.

The Section 103 rejection of claims 1-5, 8 and 9 over Sen et al (Oncogene, 14, 1997, pp 2195-2200) as evidenced by Entrez Gene (AURKA Aurora Kinase A, Last Accessed 06/03/2010) in view of Patel et al (Oncogene, 19, 2000, pp 4159-4169) and Hauf et al (Journal of Cell Biology, Vol. 161, No. 2, April 28, 2003, pp 281-294) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following and attached.

The present invention relates to the unexpected finding that cancers which overexpress Aurora A are resistant to the anti-cancer drug paclitaxel and the discovery that this resistance can be overcome by inhibition of Aurora A.

The combination of Sen, Patel and Hauf fails to teach or suggest the drug resistance of Aurora A over-expressing cells and the combination of cited art fails to teach or suggest how this barrier to cancer treatment can be overcome. The present invention addresses a problem which was previously unknown such that there would have been no motivation to have made the invention. The Federal Circuit have recently affirmed a district court finding of non-obviousness wherein there was, in a similar manner, no motivation in the art to have made the claimed invention. See In re Omeprazole, 536 F.3d 1361, 1381 (Fed. Cir. 2008) ("The court found that a person of

skill in the art would not have seen a reason to insert a subcoating in the prior art formulation shown in Example 12 of the '495 European application. The court's finding was based on Apotex's failure to demonstrate that a person of skill in the art would conclude that a negative interaction would take place between the enteric coating and the drug core.").

In the absence of any recognition in the prior art that over-expression of Aurora A in a cancer causes paclitaxel-resistance, one of ordinary skill in the art had no reason or motivation to treat cancer patients receiving paclitaxel with an aurora A inhibitor, thereby incurring additional expense and risking additional side effects. Because the problem which suggests the use of aurora A inhibitors was previously unknown, the claimed method would not have been obvious.

Furthermore, the applicants submit, with due respect, that the Examiner's rationale in making the obviousness rejection is based on some misunderstandings of the cited documents. The applicants submit that a *prima facie* case of obviousness has not been established. In particular, the Examiner states;

> "...both paclitaxel and Hesperadin are directed to exiting cells from mitosis wherein the exiting cell is in an aberrant or improper condition. While the two drugs might utilize different mechanisms of action, one of ordinary skill in the art, given the teachings of Sen, Patel, and Wang would arrive at a combination of paclitaxel and Hesperadin with a reasonable expectation that the cells would exit mitosis in an aberrant or improper condition, which is preferred for breast

> cancer cells." See pages 6-7 of the Office Action dated June 11, 2010[1].

The Examiner is incorrect in stating that paclitaxel is directed to exiting cells from mitosis wherein the exiting cell is in an aberrant or improper condition. For example, the Examiner states that:

> "Patel teaches that paclitaxel is a microtubule-stabilizing agent, wherein cells exit mitosis aberrantly and fractionate into hypodiploid populations during cell cycle analysis (see entire document, for instance, page 4163, first column, first paragraph)". See page 5 of the Office Action dated June 11, 2010

Paclitaxel does not exert its anti-cancer effects by inducing cells to exit mitosis aberrantly. It is clear from Patel that aberrant mitosis only occurs when very low doses are administered and is not related to the induction of apoptosis. For example, Patel states on Page 4163 col 1 that;

> "At < 9 nM drug concentration, paclitaxel acts by retarding or inhibiting progression through mitosis, thus altering microtubule dynamics. At these concentrations, cells exit mitosis aberrantly and fractionate into hypodiploid populations during cell cycle analysis... At >9 nM drug concentration, paclitaxel increases microtubule polymer mass, terminal G2/M arrest and cell death with a concomitant decrease in hypodiploid cells..." (Emphasis added).

In other words, cell cycle arrest and cell death occur at higher concentrations of paclitaxel (> 9 nM). At very low concentrations (< 9 nM), cell death does not occur and the cell cycle continues, albeit with increased numbers of hypodiploid cells.

[1] The Examiner is requested to clarify the reference to "Wang" in the event the rejection is maintained as the statement of the rejection on page 5 of the Office Action does not include a "Wang"

This is confirmed by Patel on page 4164, which states as follows:

> "It was demonstrated previously that rates of paclitaxel-induced apoptosis directly correlate with number of G2/M arrested cells rather than number of hypodiploid cells"

Further confirmation of the understandings of one of skill in the art that paclitaxel kills cancer cell by inducing cell cycle arrest and apoptosis is provided by the concurrently-filed Declaration by Professor Venkitaraman.

Patel therefore explicitly teaches that cell death correlates with the cell cycle arrest which is induced by higher concentrations of paclitaxel and does not correlate with the hypodiploid cells which is induced by very low concentrations of paclitaxel.

One of ordinary skill in the art seeks to treat cancer by killing cancer cells. It is clear from the teaching of Patel that killing cancer cells using paclitaxel involves inducing cell cycle arrest and apoptosis. Neither Patel nor Sen nor Hauf attribute any anti-cancer effect to the induction of aberrant mitosis exit or an increase in hypoploidy. Indeed, one of ordinary skill might consider that aberrant mitosis exit would have pro-cancer and not anti-cancer effects.

The ordinarily skilled person would not have been motivated to induce aberrant mitosis exit as a means of treating cancer, as asserted by the Examiner. This is not an objective which would have been useful in cancer treatment. Nor is there any teaching in Patel, Sen or Hauf to suggest that it might have been. Instead, the ordinarily skilled person would employ paclitaxel at doses which induce cell cycle arrest and cell death in accordance with the conventional use of paclitaxel.

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reference.

Furthermore, there is no teaching in Patel nor Sen nor Hauf that hesperadin has any significant effect on cell death. Since there is no teaching that hesperadin exerts any effect useful in cancer treatment, there would have been no motivation for the ordinarily skilled person to administer hesperadin and paclitaxel together.

In fact, Hauf explicitly teaches away from the use of hesperadin and paclitaxel together. Hauf specifically states in the legend to figure 8 that:

> "Hesperadin quickly overrides the mitotic arrest induced by taxol"

Hauf further states the following on page 288:

> "Surprisingly, when cells arrested with taxol were treated with Hesperadin, they exited mitosis within 1 h (Fig. 8, B and D). This observation, and our finding that Aurora B inhibition stabilizes syntelic attachments, raised the possibility that Hesperadin treatment turned off checkpoint signaling in taxol-treated cells because all kinetochores progressively accumulated stably attached microtubules."

Hauf therefore teaches that cells treated with paclitaxel undergo cell cycle arrest and apoptosis, but hesperadin overrides this effect and allows the cell cycle to continue.

This is confirmed by the concurrently filed Venkitaraman Declaration.

By treating cancer cells with paclitaxel, the skilled person intends to induce cell cycle arrest and apoptosis. Hauf explicitly teaches that administering hesperadin with paclitaxel *reduces* the amount of cell cycle arrest and apoptosis induced by the paclitaxel (i.e., hesperadin reduces the anti-cancer effect of paclitaxel). In view of this clear teaching, one skilled in the art would not have administered these two compounds together.

In order to administer hesperadin and paclitaxel together as asserted by the Examiner, the skilled person would have had to act directly contrary to the teaching of Hauf. The Examiner has failed to provide any reason why the ordinarily skilled person would have done same.

MPEP § 2143.01 V states as follows:

> "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)"

In the present case, combining paclitaxel with hesperadin would reduce the apoptotic effect of paclitaxel and therefore render it unsatisfactory for its intended purpose of treating cancer. There is therefore no suggestion or motivation from Hauf to have administered paclitaxel with hesperadin.

The ordinarily skilled person would not therefore have attempted, in view of Hauf and Patel, to administer hesperadin and paclitaxel together to treat any form of cancer, and this deficiency is not remedied by Sen.

Neither Sen, Hauf nor Patel would have led an ordinarily skilled person towards the treatment of Aurora A overexpressing cancers. The Examiner appears to interpret Sen as teaching that all human breast cancer exhibits an amplified and overexpressed amount of Aurora A. However, the applicants submit that this is not the case. Sen reports on an investigation of three cancer cell lines, BT474, MCF10 and SKBR3 and reports that the BTAK gene (Aurora A) is amplified in these cell lines. One or ordinary skill in the art would conclude from Sen that *some* breast cancers overexpress Aurora

A, and not that human breast cancer in general overexpresses Aurora A. This is clear from page 2195 of Sen, which explicitly states as follows:

> "Among the novel sites of amplification identified, chromosomal region 20q11-q13 was detected in about 12-18% of primary breast tumours and 40% of breast tumour cell lines."

In other words, 82-88% of primary breast tumours show no amplification of the chromosomal region containing the BTAK gene. BTAK/Aurora A is not therefore overexpressed in the majority of breast cancers.

The combination of Hauf, Sen and Patel provides no motivation to attempt to treat cancers with hesperadin and paclitaxel. In fact, the combination includes an explicit teaching away from the combination of hesperadin and paclitaxel to treat cancer. Furthermore, the combination of Hauf, Sen and Patel fails to provide motivation to identify and treat only those cancers which overexpress aurora-A, rather than cancers generally.

Withdrawal of the Section 103 rejection is requested.

The Section 103 rejection of claim 6 over Sen et al as evidenced by Entrez Gene in view of Patel et al, Hauf et al and Slamon et al (New England Journal of Medicine, Vol. 344, No. 11, pp 783-792) is traversed. Reconsideration and withdrawal of the rejection are requested for the above noted reasons with regard to the rejection of claim 1, from which claim 6 depends, as the teachings of the additionally cited reference fails to overcome the deficiencies of the combination of Sen, Patel and Hauf.

The Section 103 rejection of claim 7 over Sen et al as evidenced by Entrez Gene in view of Patel et al, Hauf et al and Obermiller et al (Breast Cancer Research 2000, 2:28-31) is traversed. Reconsideration and withdrawal of the rejection are requested for the above noted reasons with regard to the rejection of claim 1, from which claim 7 depends, as the teachings of the additionally cited reference fails to overcome the deficiencies of the combination of Sen, Patel and Hauf.

The application is submitted to be in condition for allowance a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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